REMARKS

Foremost, Applicants would like to make several clarifications:

(1) On page 3, lines 7-9, of the Action, the Examiner states, "However, as explained in paragraph 9 of the Rule 132 [Declaration] of Dr. Michael Ross, MD, the additional data in the Rule 132 declaration of Dr. Khamar are nothing more than 'minor details.'" However, the Rule 132 Declaration of Dr. Ross was inadvertently not submitted with the response filed January 22, 2008. Thus, the Examiner has *not* considered Dr. Ross' Declaration which is attached herewith.

(2) In the paragraph bridging pages 3 and 4 of the pending Action, the Examiner states that the specification discloses 8 different preparations of Mycobacterium w pharmaceutical compositions, but "neither the specification nor the Declaration of Dr. Khamar specifies which of the types was actually utilized." Dr. Khamar herewith provides a Supplemental Rule 132 Declaration clarifying that composition of Example 1A was actually utilized in Examples 4-6 while the compositions of Examples 1A and 1D were utilized in Examples 7 and 8. In fact, this information was provided in the substitute specification filed with the Amendment of June 11, 2007.

(3) The statements regarding inventorship and ownership in (a) Dr. Khamar's Declaration filed with the response of January 22, 2008, (b) Dr. Ross' Declaration executed on December 11, 2007, (enclosed herewith) and (c) Dr. Lamberti's Declaration executed on December 31, 2007, (enclosed herewith) are in accordance with the original Applicant Data Sheet in the record at the time of execution of the declarations of Dr. Khamar, Dr. Ross and Dr. Lamberti. However, subsequent to the execution of the declarations of Dr. Khamar, Dr. Ross and Dr. Lamberti, Applicants have filed Correction of Inventorship and a new Assignment.

Please note that inventors after filing the Correction of Inventorship are Rajiv Indravadan Modi and Bakulesh Khamar, the first named inventor being Rajiv Indravadan Modi, and the current assignee is Cadila Pharmaceuticals Limited.

Claim Rejection - 35 U.S.C. § 112

The rejection of claims 22- 48, under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement, was maintained for reasons of record. This rejection is respectfully traversed.

The adequacy of the specification in the United States is governed by 35 USC Section 112, first paragraph, which provides:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Thus, in the United States, the specification must sufficiently describe the claimed invention so that it conveys that the inventors had possession of the claimed invention *and* describe the claimed invention so that a person skilled in the art is enabled to make and use the invention (*University of Rochester v G D Searle & Co, Inc*, 358 F3d 916, 921 (Fed Cir 2004)).

The enablement provision of the UK Patents Act requires that "[t]he specification of an application shall disclose the invention in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the art." See UK Patents Act (1977), Section 14(5).

Foremost, Applicants want to respectfully submit that the counterpart UK application has been allowed by the UK Patent Office as a patent with Patent Number GB2392620 having substantially the same claims as those in the pending US application *without* any rejection for lack of enabling disclosure. See attached copy of the granted UK patent.[1] While Applicants understand

[1] Claim 1 of Patent Number GB2392620 recites:

that the USPTO and the UK Patent Office are independent patent granting authorities, Applicants respectfully submit that the USPTO should at least consider the evidence that the counterpart UK application has been granted as being ***persuasive*** for overcoming the enablement rejection in the US application as the UK patent law also has a similar enablement standard ("clear enough and complete enough for the invention to be performed by a person skilled in the art") as that under the US patent law.

In the US, a specification satisfies the enablement requirement where the specification teaches a person skilled in the art to make and use the invention without undue experimentation (*Amgen Inc v Hoechst Marion Roussel, Inc*, 314 F3d 1313, 1334 (Fed Cir 2003)). The specification need not explicitly teach every detail in making and using the invention. "An inventor need not, however, explain every detail since he is speaking to those skilled in the art." *DeGeorge v. Bernier* 768 F.2d 1318, 1323 (C.A.Fed., 1985)(citing *In re Howarth*, 654 F.2d 103, 105 (CCPA 1981). A disclosure is sufficient even if it would require that one skilled in the art conduct some experimentation. *White Consolidated Industries, Inc. v. Vega Servo-Control, Inc.*, 713 F.2d 788, 791 (Fed. Cir. 1983). "The amount of required experimentation, however, must be reasonable." *Id.* See also, *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991)("That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue.'").

In order to determine whether the needed experimentation is undue, the Federal Circuit has stated that the USPTO must consider the following factors (hereinafter "the *Wands* factors"): (1) the quantity of experimentation necessary to practice the invention; (2) the amount of direction or guidance provided; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of prior art; (6) the relative skill of those in the art; (7) the predictability or

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Use of mycobacterium w, or constituents of mycobacterium w prepared by cell disruption, solvent extraction, or enzymatic extraction, for the preparation of a pharmaceutical composition for use in the treatment, management or prevention of obstructive lung disease.

unpredictability of the art; and (8) the breadth of the claims (*In re Wands*, 858 F2d 731, 737 (Fed Cir 1988)).

Subsequent decisions have addressed how the *Wands* factors should be applied. First, although *In re Wands* concerned enablement per se (as alleged by the Examiner in the present application), the Federal Circuit has sanctioned the use of these factors to determine the scope of enablement. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). However, none of the decisions applying the *Wands* factors has discussed how each factor should be weighed. As a result, it is difficult for an inventor to know how much disclosure is necessary to enable the full scope of his claims. Second, the Federal Circuit has held that the *Wands* factors are merely illustrative. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991). Therefore, a court is free to choose which factors to examine, to create new factors to apply, or to ignore factors that are present. Third, although *In re Wands* was an ex parte case, the factors also apply to inter partes litigation because in both instances, the proper inquiry focuses on what would have been enabled at the time of filing. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371-72 (Fed. Cir. 1999).

Applicants respectfully apply the *Wands* factors to the present application.

(1) The quantity of experimentation necessary to practice the invention

The factor "quantity of experimentation needed" is a misnomer. Discussing *In re Wands*, the Federal Circuit in *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998), stated that undue experimentation is "not merely quantitative," and that a considerable amount of experimentation is permissible.. The resolution of this apparent contradiction is that the court is concerned with the amount of *non*-routine experimentation, *not* the total quantity of experimentation. Some technologies are inherently unpredictable and require much repetition, even with a detailed disclosure. *Id.*

Applicants submit that the specification provides clear and sufficient guidance to one of ordinary skill in the art on how to make and/or use the claimed invention such that the amount of

non-routine experimentation needed to practice the claimed invention would be negligible. Specifically, the present application includes numerous references to human hosts. (See e.g., Examples 4-8). Indeed, all of the examples are illustrated with human patients. Further, regarding the dosage and composition, Example 1 provides 10 different recipes for 0.1 ml therapeutic doses. Example 6 teaches giving patients 0.1 ml doses at a rate of 1 per week. Additionally, Example 2 teaches the preparation of a pharmaceutical composition in great detail. Regarding frequency and duration, Example 4 teaches treating the patient once a week for four weeks while Example 7 teaches treating patients according to a conventional regimen for three months. Regarding the route of administration, Example 4 teaches intradermal administration. The specification also teaches that asthma medications may be inhaled or taken orally with the preferred method being inhalation. (See pages 2-3 of the instant application). *One of ordinary skill in the art reading the specification would clearly understand that typical treatment conditions would comprise giving a patient approximately 0.1 ml doses once a week for four weeks to three months.*

(2) The amount of direction or guidance provided

As explained in paragraph 5 of the attached Rule 132 Declaration of Dr. Lamberti, who is a pulmonary medicine specialist, to which this invention relates to, "one of ordinary skill in the art of the present invention, i.e., *a pulmonary medicine specialist, at the time of the filing of the '211 application would have been able to practice the claimed invention after reading the application.* Specifically, regarding the composition of the dosages, I note that Example 1 teaches several therapeutic compositions in which each dosage includes 0.1 ml of the therapeutic agent. Example 1 further teaches that compositions A, B, C and J contain heat killed whole cell Mycobacterium w, composition D contains extract of Mycobacterium w after sonication (i.e., after cell disruption), and compositions E to I contain cell fraction extracted Mycobacterium w." [Emphasis added.]

(3) The presence or absence of working examples

Although the Federal Circuit has indicated that it believes this factor is important, it has not provided much guidance on how it should be applied. The question of how many and what

kinds of examples are needed is left unanswered. *In re Goodman*, 11 F.3d 1046, 1050-51 (Fed. Cir. 1993) (holding that a single example is not enough to enable a broad genus); see also *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993) (holding that a single example merely invites experimentation). In *Amgen, Inc. v. Hoechst Marion Roussel*, the Federal Circuit states that a single example is indeed enough, provided that "any gaps between the disclosures and the claim breadth could be easily bridged." *Amgen, Inc. v. Hoechst Marion Roussel*, 314 F.3d 1313, 1336 (Fed. Cir. 2003).

The specification discloses ***8 examples*** (Examples 1 to 8), not just one or two. Example 1 contains different pharmaceutical compositions of the therapeutic agent containing Mycobacterium w. Example 2 discloses the process of preparing the pharmaceutical composition. Example 3 discloses characteristics of constituents of Mycobacterium w analyzed by HPLC. Examples 4-8 disclose the method of administering the pharmaceutical compositions to patients and effect of administering the pharmaceutical compositions.

Furthermore, as the Examiner's contention has been that the specification does not teach "the actual composition administered to the patients (whole cells, disrupted cells, cell fractions, etc.), the dosage administered, the route of administration, and the frequency of administration," (see page 6, lines 1-3, from the bottom of the Action of March 9, 2007, Dr. Lamberti prepared a chart shown in paragraph 6 of his attached Rule 132 Declaration to determine what the application explicitly states in Examples 4 and 6, and identify gaps, if any, in the disclosure of the application. He concludes the following in paragraphs (7) to (11) of his Rule 132 Declaration:

> (7) In short, both Examples 4 and 6 state that the composition contains "Mycobacterium w" but does not explicitly state "Mycobacterium w as provided in Example 1A." In addition, Example 4 does not explicitly state that the dosage was 0.2 ml per week initially followed by 0.1 ml per week and Example 6 does not explicitly state that the route of administration was through a nebulizer. Having identified these "gaps" in Examples 4 and 6, I now provide my analysis as an expert in pulmonary medicine, which is the field of this invention, as to why these "gaps" would have been obvious to me.

(8) Regarding the "gap" in composition, I notice that Examples 4 and 6 state that the compositions contain "Mycobacterium w" but does not explicitly state which composition of Example 1 was specifically used. However, Example 1 provides several compositions as Examples 1A to 1J. Thus, based my understanding of this art, I would recognize that Examples 4 and 6 could be carried out using any of Examples of 1A to 1C, which contain 0.5×10^9 heat killed Mycobacterium w, Example 1D, which contains 1×10^9 sonicated Mycobacterium w, Examples 1E to 1I, which contain 1×10^9 solvent extracted Mycobacterium w, or Example 1J, which contains 0.5×10^7 heat killed Mycobacterium w. The concentration of Mycobacterium w in Examples 1A to 1J is 0.5×10^7, 0.5×10^9 or 1×10^9. In light of Examples 1A to 1J, it would have been obvious to select a concentration of Mycobacterium w of 0.5×10^7 for patients who have a lower degree of respiratory impairment, to use a concentration of Mycobacterium w of 0.5×10^9 for patients who have a moderate degree of respiratory impairment, and to use a concentration of Mycobacterium w of 1×10^9 for patients who have a higher degree of respiratory impairment. In fact, as a first choice, I would select Example 1A having a concentration of Mycobacterium w of 0.5×10^9, as it is the first exemplary composition in the specification and because the concentration of Mycobacterium w of 0.5×10^9 falls within the upper and lower limits of concentrations of Mycobacterium w of 0.5×10^7 and 1×10^9 disclosed in Examples 1A to 1J. In short, based on the disclosure of the '211 application, it would have been obvious to me to select "Mycobacterium w as provided in Example 1A" having a concentration of Mycobacterium w of 0.5×10^9 in the compositions of Examples 4 and 6.

(9) Regarding the "gap" in dosage in Example 4, I notice that each one of Examples 1A to 1J states, "Each dose of 0.1 ml of therapeutic agent." Typically, the intradermal dose of a medication is 0.1 ml. It is common in pulmonary medicine to utilize a "loading" or priming dose of a medication followed by a maintenance dose. As a practitioner of pulmonary medicine, I consider it routine to give a dosage of 0.2 ml, followed by a dosage of 0.1 ml, when the dosage is administered intradermally, as was done in Example 4 according to Dr. Khamar's Declaration.

(10) Regarding the "gap" in the route of administration in Example 6, I notice that Example 4 states that the patient "was given Mycobacterium w intradermally at the interval of one week," and that pages 2-3 of the specification teach that asthma medications may be inhaled or taken orally. In fact, it is well-known that pulmonary

medications can be administered intradermally, inhaled through a nebulizer, or taken orally. Furthermore, it is well known in pulmonary medicine that all of the three routes are interchangeable and can provide an effective therapy. The specific route of administration depends mostly on patients' choice, rather on any other factors. Thus, even though Example 6 does not explicitly disclose that Mycobacterium w was administered using a nebulizer as explained in Dr. Khamar's Declaration, this "gap" is not a flaw in the specification that would prevent me or other pulmonary medicine specialists from practicing this invention as I often use different routes based on patients' choice as these routes are interchangeable.

(11) Based on the cited specific compositions, dosages, routes of administration, and frequencies of administration in the '211 application, I conclude that one of ordinary skill in the art at the time of the filing of the '211 application having read the application would have been able to practice the claimed invention without undue experimentation. One of ordinary skill in the art of pulmonary medicine would understand (1) that the appropriate therapeutic dosage is typically 0.1 ml of Mycobacterium w, but could also be twice this dosage for patients with a higher degree of respiratory impairment, (2) the dosage may include whole cells, sonicated cells, or extracted cell fractions, (3) the composition could be administered intradermally or by nebulizer approximately once per week, and (4) treatment could be continued from four weeks to three months, or longer or shorter depending on the response exhibited by the patient to the treatment.

(4) The nature of the invention

This factor is generally never referred to explicitly in prior Federal Circuit cases. In one of the few instances in which it was explicitly mentioned, *Plant Genetic Systems, N.V. v. Dekalb Genetics Corp.*, 315 F.3d 1335, 1339 (Fed. Cir. 2003), the court found the consideration of this issue to be moot.

The nature of this invention relates to a method of treating, managing or preventing obstructive lung disease comprising administering to a patient a pharmaceutical composition comprising an effective amount of (a) Mycobacterium w or (b) a constituent of Mycobacterium w.

(5) The state of prior art

Prior art can be used to fill in small gaps in the disclosure though prior art is not a substitute for a basic enabling disclosure. *Genentech v. Novo Nordisk*, 108 F. 3d 1361, 1366 (Fed. Cir. 1997). The Federal Circuit in *LizardTech , Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336 (Fed. Cir. 2005), has explained:

> The patent specification is written for a person skill in the art, and such a person comes to the patent with the knowledge of what has come before. ... Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation. [Citations omitted.]

As explained in paragraph 7 of Dr. Lamberti's attached Rule 132 Declaration, the "'gaps' [in the disclosure] would have been obvious" to persons of ordinary skill in the art. Reviewing the present application in the context of the law as stated in *LizardTech*, Applicants respectfully submit that Dr. Lamberti, a person of skill in the art of pulmonary medicine, is convinced as evidenced by his attached Declaration that the specification provides enough details to enable him to make and use the invention without undue experimentation.

(6) The relative skill of those in the art

The field of art of the claimed invention is pulmonary medicine. The level of ordinary skill in pulmonary medicine is that of "a pulmonary medicine specialist" such as Dr. Lamberti whose CV is attached to his Rule 132 Declaration. See paragraph 5 of Dr. Lamberti's Rule 132 Declaration. The relative skill of those practicing pulmonary medicine is very high such that the minor "gaps" in the examples of the specification "would have been obvious" to them. See paragraph 7 of Dr. Lamberti's Rule 132 Declaration.

(7) The predictability or unpredictability of the art

MPEP 2164.03 states:

> The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification.
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> ***
>
> The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art.

In the paragraph bridging pages 3 and 4 of the pending Action, the Examiner states that as the specification discloses 8 different preparations of Mycobacterium w pharmaceutical compositions, but because "neither the specification nor the Declaration of Dr. Khamar specifies which of the types was actually utilized," there is insufficient information to enable the claimed invention. Thus, the Examiner seems to imply that it would have been unpredictable to persons skilled in the art to select one Mycobacterium w pharmaceutical composition from the 8 different preparations of Mycobacterium w pharmaceutical compositions. The Supplemental Declaration of Dr. Khamar (enclosed herewith) clarifies that the composition of Example 1A was utilized in Examples 4-6 and the compositions of Examples 1A and 1D were utilized in Examples 7 and 8 . Also, paragraph 8 of Dr. Lamberti's Declaration (reproduced above) explains that the selection of Example 1A from the 8 different preparations of Mycobacterium w pharmaceutical compositions disclosed in the specification would been an obvious and predicable choice to a person of ordinary skill in the art. "*In short, based on the disclosure of the '211 application, it would have been obvious to me to select 'Mycobacterium w as provided in Example 1A' having a concentration of Mycobacterium w of 0.5 x 10^9 in the compositions of Examples 4 and 6.*" [Paragraph 8 of Dr. Lambert's Declaration; emphasis added.]

(8) The breadth of the claims

Independent claim 22 recites, "A method of treating, managing or preventing obstructive lung disease comprising: administering to a patient a pharmaceutical composition comprising an effective amount of (a) Mycobacterium w or (b) a constituent of Mycobacterium w." This claim is limited to specifically treating, managing or preventing lung disease, not any disease, with an effective amount of (a) Mycobacterium w or (b) a constituent of Mycobacterium w. Independent claim 23 further recites that the disease is asthma. Independent claim 48 further recites "wherein the constituent of Mycobacterium w is prepared by cell disruption, solvent extraction, or enzymatic extraction." In short, the breadth of the claims is commensurate with the enabling disclosure.

Conclusion

The issue of enablement is highly fact-specific, without any bright line rules for guidance. This ad hoc approach is described by Judge Newman in her dissent in *In Re Wands*, where she states, "As illustrated in extensive precedent on the question of how much experimentation is 'undue,' each case must be determined on its own facts." *In re Wands*, 858 F.2d 731, 742 (Fed. Cir. 1988).

In the present application, based on the facts of this case, Applicants respectfully submit that the UK Patent Office has reviewed the counterpart UK application and granted claims of the same scope as those pending in the US application. Also, Dr. Lamberti, a pulmonary medicine specialist, who is a person of skill in the art related to the claimed invention, has reviewed the data and details disclosed in the specification and concluded that the specification teaches persons of skill in the art how to make and use the claimed invention.

MPEP 2164.05 states:

> Once the examiner has weighed all the evidence and established a reasonable basis to question the enablement provided for the claimed invention, the burden falls on applicant to present persuasive

> arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *In re Brandstadter*, 484 F.2d 1395, 1406-07, 179 USPQ 286, 294 (CCPA 1973). The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art. [Underlining in original.]

Applicants respectfully submit that Applicants have met their burden to present persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. As explained in MPEP 2164.05, the evidence provided by Applicants need merely be convincing to one skilled in the art. Applicants believe that the evidence in the form of the grant of the counterpart UK application with substantially similar claims as those in the present application and the Declaration of Dr. Lamberti should convince one skilled in the art that the application provide enabling disclosure for one skilled in the art to make and use the claimed invention.

In view of the above, Applicants respectfully submit that the enablement rejection should be withdrawn.

Applicants believe the pending application is in condition for allowance.

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